Second Edition

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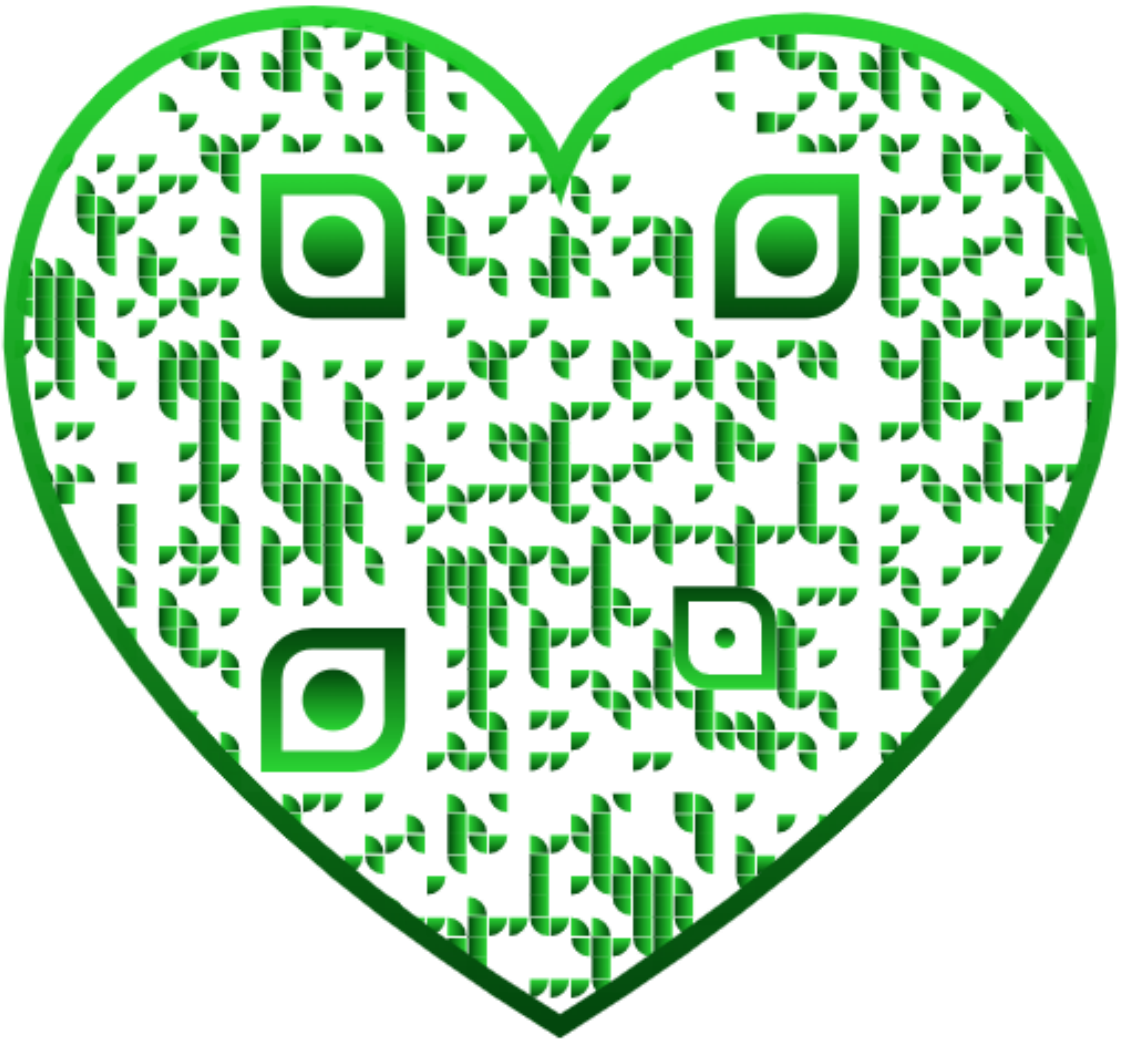
MINISTRY OF HEALTH MALAYSIA

PHARMACOECONOMIC GUIDELINES

FOR MALAYSIA

MINISTRY OF HEALTH MALAYSIA



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Statement of Intent
These guidelines will replace the Pharmacoeconomic Guideline for Malaysia 2012.

Disclaimer
These guidelines are meant to standardise the conduct of local pharmacoeconomic research and budget impact analysis for medicine listing submissions to the Ministry of Health Malaysia. Compliance with these guidelines does not ensure a positive recommendation for any policy decision.

Foreword

Greetings to all,

First of all, I would like to extend my heartiest congratulations to the Pharmaceutical Services Programme, Ministry of Health Malaysia, for its success in producing the new edition of Pharmacoeconomic Guidelines for Malaysia 2019. This is timely, and it serves the current needs of the healthcare systems, considering that most of these systems continue to face rising budgetary pressures and constraints of resources. Thus, healthcare payers need to select only high value medicines by using standard methods and decision-making framework to outweigh the amount of money invested relative to health benefits gained while at the same time making sure all medicines received by patients are of high quality, safe and cost-effective.

Pharmacoeconomics is indeed a growing field across the globe, and it is not new in Malaysia. Since the introduction of the first edition of these guidelines in 2012, many more researches have been conducted, and local data have been generated both from the public sector, including the health and education fields, as well as from the private sector, including the pharmaceutical industry and independent consultants. However, the quantum is still insufficient. I acknowledge the challenges faced by those working in this area such as lack of policy and guidance, unavailability of data and lack of transparency with regard to both health outcomes and costs, and also the number of competent experts in the country.

I really hope that the new Guidelines will be a standard guidance in conducting pharmacoeconomic studies for any party that wishes to assess the value for money of pharmaceuticals in Malaysia. We should aim to increase and update the knowledge of healthcare stakeholders so they are able to understand, conduct and apply the findings made in pharmacoeconomic studies when making rational therapeutic choices. These guidelines will also help set up a standard to ensure that all pharmacoeconomic studies in Malaysia are of high and similar quality and are also relevant to meet the needs of healthcare decision makers.

I wish to express my heartfelt gratitude to the Development Group and the Reviewers for their hard work. These Guidelines are the output of collaboration between local experts in pharmacoeconomic from the Ministry of Health, Ministry of Educations, Pharmaceutical Associations of Malaysia and consultants from the private sector. I wish to see continuous engagement, collaborations and continuous efforts to further improve the execution of the value-based medicine (VBM) principles for a more efficient healthcare service and optimum health outcomes to the patients. Thank you.

YBhg. Datuk Dr. Noor Hisham bin Abdullah
Director General of Health
Ministry of Health, Malaysia

Preface

Greetings to all,

Pharmacoeconomics has becoming progressively an important and fast emerging area of research in recent years. The purpose of pharmacoeconomic evaluations is to help decision makers make choices on new pharmaceutical products based on credible and valid information. By considering pharmacoeconomic evaluations in making the decisions, efficient allocation of medical resources can be made.

The first edition of these guidelines was published in 2012 with the aim to promote local research in the field of Pharmacoeconomics. Since then, I have observed progress in the field pharmacoeconomic in this country, however, I believe that it is still insufficient to aid the healthcare decision making especially in the context of Pharmaceutical Services Programme selecting medicines to be listed in national formulary. Besides, over the years, there were some updates in this field internationally and locally. The Development Group has also learnt from the previous guidelines and identified aspects that were inadequately mentioned. The Development Group has also taken into considerations new insights of various publications by international organisations and professional associations such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

For all those reasons, this is indeed the best time to come out with the new Pharmacoeconomic Guidelines for Malaysia 2019. I really hope that this approach is able to update, refresh and give new momentum to all stakeholders to intensify their works in this field. With these updated guidelines, it is hoped to provide enlightenment to the relevant stakeholders and researchers and to promote the production of more timely, reliable, consistent and relevant pharmacoeconomic evaluations in Malaysia. I encourage such evaluations to be carried out at various levels of healthcare settings to facilitate decision making.

I would like to express our endless gratitude to the Director General of Health, Malaysia, for his permission to publish these guidelines. The Pharmaceutical Services Programme, Ministry of Health, is grateful to the members of the Development Group and deeply indebted to the Internal and External Reviewers who have devoted substantial time, expertise and commitment in the development of these guidelines. I am also grateful for the considerable contributions of the Pharmaceutical Association of Malaysia (PhAMA) for their valuable inputs to these guidelines. Thank you.

YBrs. Dr. Ramli bin Zainal
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AIM

To encourage the production of timely, reliable, consistent and relevant economic evaluation of pharmaceutical interventions in the Malaysian healthcare system.

OBJECTIVES

The objectives of these pharmacoeconomic guidelines are to:

- set a standard for quality, transparent and uniformed economic evaluations and budget impact analyses (BIAs) of pharmaceutical interventions in Malaysia;
- update the methodological guidance based on the latest developments in the field of health economics and adopt these for the Malaysian setting;
- promote the generation of local primary data in Malaysia by guiding potential researchers to conduct pharmacoeconomic evaluations; and
- facilitate critical appraisals of pharmacoeconomic studies and BIA reports for the Malaysian context.

TARGET USERS

These guidelines are intended for use by researchers, pharmaceutical companies, health economists, health professionals and all those who are involved in the conduct or use of pharmacoeconomic evaluations and BIAs in Malaysia.

GUIDELINES STRUCTURE

These guidelines comprise two main sections: (1) economic evaluation and (2) BIA. For the first section on economic evaluation, these guidelines are different from the previous edition as they combine both the conceptual definitions and methodologies in one section. Additional focus is given on the methodologies in this edition. BIA is discussed separately in the second section to differentiate it from economic evaluations and to provide clearer overview of its relevance and importance for policy decisions. Explanations and recommendations are provided in each section of these updated guidelines. The recommendations for an ideal method to be used in both economic evaluation and BIA are summarised in Table of Reference Cases. Definition of terms can be found in the Table of Abbreviation which is located before the main contents while the key features for both economic evaluation and BIA are enclosed in the Appendices.

GUIDELINES DEVELOPMENT PROCESS

The development of these guidelines was carried out in two phases. The first phase started with a workshop to establish the Development Group consisting of twelve pharmacists with a background in health economics. Nine of them are from the Ministry of Health (MoH), three from the Ministry of Education (MoE), one consultant from the private sector and one representative from the Pharmaceutical Association of MaIaysia (PhAMA).

During the workshop, discussions focused on the setting up of the outline and concept of the updated guidelines. Then brainstorming sessions were carried out to determine the contents. This was followed by the drafting of the contents. Assignments were conducted in three separate groups.

The section on economic evaluation was drafted based on the review of pharmacoeconomic guidelines from other countries. Modifications were made where applicable to suit local settings. Literature searches were also performed to fill in information gaps. Meanwhile, the section on BIA was prepared largely based on the report by ISPOR 2012 BIA Good Practice II Task Force (Sullivan et al., 2014), an updated publication by Mauskopf et al., 2016 as well as the practical experiences in the local setting.

Each group presented its first drafts for deliberations by other workshop participants. Revisions were made based on subsequent feedback and discussions. Efforts were made to achieve consensus, and the Pharmacy Practice & Development Division of the Ministry of Health has the final say on the final draft of these guidelines. The first draft of each section was then compiled by the Secretariat from the Formulary Management Branch to produce the second draft.

The second phase involved the process of reviewing the second draft of the guidelines by both internal and external reviewers. Then the Secretariat collected all comments and feedback to further improve the draft. Finally, the third draft was reviewed and published.

LIST OF ABBREVIATIONS

Table 1: List of abbreviations

Abbreviation	Definition
BIA	Budget Impact Analysis
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CET	Cost-Effectiveness Threshold
CMA	Cost-Minimisation Analysis
CUA	Cost-Utility Analysis
DALY	Disability-Adjusted Life Years
DCA	Drug Control Authority
EMA	European Medicines Agency
EQ-5D	EuroQol 5D
FDA	Food Drug Administration
HRQoL	Health-related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ISPOR	International Society of Pharmacoeconomics Outcomes Research
MADRAC	Malaysian Adverse Drug Reactions Advisory Committee
MeSH	Medical Subject Headings
MoH	Ministry of Health
MoE	Ministry of Education
MTC	Mixed Treatment Comparison
NPRA	National Pharmaceutical Regulatory Agency
PhAMA	Pharmaceutical Association of Malaysia
PICO	Patient/Population/Problem, Intervention, Comparator and Outcome
PSA	Probabilistic Sensitivity Analysis
PSP	Pharmaceutical Services Programme
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SG	Standard Gamble
SMDM	Society for Medical Decision Making
TTO	Time-Trade Off
WTP/QALY	Willingness-To-Pay Per Quality-Adjusted Life Years

HIGHLIGHTS OF SECOND EDITION

Several changes were incorporated in these new guidelines such as additional information or amendments to the previous guidelines. The major changes in the contents are listed in Table 2.

Table 2: Highlights of content changes

Content	Changes
Problem Statement	Formulating problem statement by using a brief description of PICO
Analytic Technique	Analytical approach either trial-based or model-based
Retrieval of Effectiveness Evidence	Prioritisation of data, search strategy, source for obtaining data
Measuring Outcomes	Valuation method of HRQoL
Resource Use and Cost	Description of costs according to the study perspective, resource valuation and costing method
Presentation of Results	Formula for ICER
Cost-effectiveness Threshold	Discussion on approaches to determine CET with their pros and cons and currently available reference for local setting
Sensitivity Analysis	Description of type of sensitivity analysis
Modelling	Good practices of modelling
Generalisability	Discussion on applicability of the economic evaluation results to local practice
Reporting	Good practices of reporting an economic evaluation
Budget Impact Analysis	Details of the key steps in conducting BIA

REFERENCE CASES

A reference case suggests an ideal structure of an economic evaluation or BIA for submission to the MoH Malaysia. It includes all of the recommended methods and contents for each component. The reference cases for economic evaluations and BIA are presented in Table 3 and Table 4, respectively.

Table 3: Reference cases for economic evaluation

Reference case	Description
Problem Statement	Brief description of PICO analysis. It must be clearly stated.
Analytic Technique	Trial-based or model-based study. CEA or CUA method.
Target Population	For whom the intervention is intended for in the clinical practice. Subgroup is used when applicable.
Perspective	Payer or budget holder in the applied setting
Time Horizon	Long enough to capture all changes in cost and outcomes of the intervention. Choice must be justified.
Selection of Comparator(s)	Most relevant alternative(s) for the proposed indication in the applied setting that is (are) most likely to be replaced by the new intervention. Choice must be justified.
Retrieval of Effectiveness Evidence	Data from higher levels of evidence i.e. RCTs, systematic reviews and meta-analyses of RCTs should be given priority.
Measuring Outcomes	Appropriate outcome measure(s) based on the disease and type of economic evaluation. QALY is useful to compare ICERs for different disease areas.
Resource Use and Cost	All relevant resources use and costs depend on the perspective of the study.
Discounting	3% for both costs and outcomes
Presentation of Results	Present as ICER

Reference case	Description
Threshold	No explicit threshold. Several published articles on the estimation of cost-effectiveness threshold in Malaysia may be used as a guide.
Sensitivity Analysis	One-way, scenario and probabilistic sensitivity analysis
Modelling	Modelling is used only when appropriate. All choices made should follow good practice guidelines and must be justified.
Generalisability	Should contain details that allow readers to appraise whether the results of the study are applicable to their settings.
Reporting	In accordance with the guidelines for good practice in reporting economic evaluations

Table 4: Reference case for BIA

Reference case	Description
Eligible Population	All patients who are likely to receive treatment with the new drug
Perspective	Payer or Budget holder
Time Horizon	5 years
Treatment Mix	Current treatment mix must include all current treatments that will undergo changes in clinical practice upon introduction of the new intervention. Established off-label uses should also be included. The change in the market share is predicted based on the future treatment mix (current and new intervention treatment mix).
Drug Related Cost	Direct healthcare costs due to the pharmaceutical intervention(s) and related clinical management. For instance, the drug acquisition cost and other drug related costs such as administration, monitoring and managing side effects or adverse events.

Reference case	Description
Disease Related Cost	Direct healthcare costs related to managing the disease such as the cost of diagnostic, monitoring, laboratory test, hospitalisation, out-patient visits and subsequent clinical sequela.
Presenting Budget Impact	Total budget and incremental cost with graphical presentation

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INTRODUCTION

An economic evaluation is a comparative analysis of different interventions or strategies with regard to both costs and consequences. Therefore, the basic tasks in conducting an economic evaluation are to identify, measure, value and compare the costs and consequences of the interventions under consideration. In cases where any of the components of the reference case is missing, for example, in an analysis in which there is no comparator being evaluated against, or missing cost/outcome data, the study will be considered as conducting a partial economic evaluation instead of a full economic evaluation. Examples of partial and full economic evaluations are given in Table 5 below. The partial economic evaluation could be an important intermediary stage in understanding cost and consequences of a treatment. However, unlike the full economic evaluation, the partial economic evaluations cannot answer efficiency questions (Drummond et al.,2015).

Table 5: Types of economic evaluation and their examples

Partial	Full
Cost minimisation analysis Cost analysis Cost description Cost-outcome description	Cost effectiveness analysis Cost utility analysis Cost benefit analysis

In contrast, BIA describes the estimated changes in the budget expenditure of a health care system after the adoption of a new intervention. The following sections discuss the characteristics and components of economic evaluations and BIA.

For ease of understanding, the term ‘economic’ is used interchangeably with ‘pharmacoeconomic’ throughout these guidelines as the scope of all the discussions is mainly on pharmaceuticals. Likewise, the term ‘economic analysis’, ‘health consequences’ and 'interventions’ are used interchangeably with ‘economic evaluation’, ‘health outcomes’ and ‘treatment’, respectively.

In the context of conducting economic evaluation or BIA for submission to the MoH, researchers are advised to prepare the framework and preliminary design first before

proceeding with the analysis. It is important to note that all aspects relevant to the analysis must be clearly described in the report and that all choices made for the analysis are justified.

A. ECONOMIC EVALUATION

1. Problem Statement

A problem statement or research question is a brief description of an issue in the form of a question which a pharmacoeconomic analysis attempts to answer. It must be stated clearly at the very beginning of the study with information on the disease such as its epidemiology, cost of illness and standard treatment options. Often, problem statement is formulated concisely by describing the problem, patient or population, intervention under study, relevant comparator(s) and outcome measure(s) of the analysis (i.e. PICO method). The primary perspective of the study may also be stated in the question.

2. Analytic Technique

2.1 Types of Economic Evaluation

i. Cost-Minimisation Analysis (CMA)

CMA may be conducted when two interventions have similar health consequences at different costs. Once the similarities of the health consequences are established by evidence, a CMA would compare all costs between the treatments to determine the option with the least cost. However, since this is not regarded as a full pharmacoeconomic evaluation, it will not be discussed in the following sections.

ii. Cost-Effectiveness Analysis (CEA)

CEA compares the relative difference of costs and consequences of different treatments. In CEA, costs are measured in monetary terms, and

health consequences are measured in natural or physical units. This analytical method is recommended when a clinical outcome parameter or improvement in life expectancy is the main goal of the treatment. Final clinical outcomes are commonly preferred over intermediate or surrogate outcomes. However, should an intermediate or surrogate outcome be used, justification is required. The use of a surrogate outcome is only advisable when its link to the final clinical outcomes of interest is well-established.

iii. Cost-Utility Analysis (CUA)

In principle, CUA is very similar to CEA except that the outcome is measured using health-related quality of life in terms of utility. It is also used when the treatment assessed has multiple patient-related outcome parameters reported in different units. This analytical method is recommended for simultaneous assessment of improvements in both quantity and quality of life due to the interventions. Quality Adjusted Life Years (QALYs) is an outcome measure that combines quantity and quality of life (utility). Utility is commonly measured using tools and instruments such as the EQ-5D (see Section 8.3). Correspondingly, CUA has increasingly become the standard for economic evaluation in the healthcare sector as it allows for the comparison of incremental cost and outcomes across different health conditions.

iv. Cost-Benefit Analysis (CBA)

Cost Benefit Analysis (CBA) compares two treatment options when both costs and benefits are expressed in monetary terms. There are various methodological challenges in conducting a CBA, including ethical and technical challenges associated with assigning monetary values to health outcomes.

Table 6: Summary of different types of pharmacoeconomic analysis

Type of Analysis	Measurement of Costs	Measurement of Outcomes	Example of Outcomes
CEA	Monetary	Natural/ physical units (final, intermediate or surrogate outcomes)	Millimetres mercury to express blood pressure, event free survival or life years gained
CUA	Monetary	Multidimensional	QALYs/ DALYs
CBA	Monetary	Monetary	Monetary

2.2 Analytical approach

In any economic evaluations, the analytical approach chosen, either a trial-based or model-based evaluation, should be well justified. Ideally, the trial-based evaluation is preferred in view that it allows utilisation of local effectiveness data. However, both approaches have their own strengths and weaknesses as discussed below.

2.2.1 Trial-based Economic Evaluations

The most common trial-based economic evaluation is the evaluation alongside a randomised controlled trial (RCT). The resources use, health outcomes and utility data for a trial-based economic evaluation should be prospectively collected from the RCT trial population while the RCT is being conducted. The trial-based economic evaluation is useful when the findings are explicitly interpreted within the context of the study.

The findings generated from RCTs have high internal validity in that they are credible within the context of the trial conditions. However, trial-based studies tend to have insufficient information for the economic

evaluation as RCTs are often designed and conducted primarily to evaluate treatment efficacy.

Some of the potential weaknesses of RCT for the purpose of economic evaluations are inappropriate comparator, inadequate sample size, a limited time horizon, occurrence of protocol-driven costs or outcomes, inappropriate outcome measures and patient selection.

2.2.2 Model-based Economic Evaluation

Models allow analysts to combine data from various sources to estimate the incremental costs and outcomes of an intervention compared to a comparator(s). The selection of data parameters for a model-based evaluation must be described and justified. Ideally, model parameters should be identified from the literature based on a systematic search.

The model-based economic evaluation can project extended time horizons including the lifetime horizon such as relevant comparators (different from the ones typically found in published trials); extrapolation of intermediate outcomes for the final health outcomes; consideration of various externalities associated with a treatment delivery or effectiveness, and usage of outcome data from multiple trials through systematic review and meta-analysis methods.

Some of the most commonly used models in economic evaluations are the decision tree models, state-transition models (also known as Markov models), discrete event simulations and dynamic transmission models.

The main limitation of modelling is that assumptions need to be made in order to combine data from different sources, particularly the assumption that the model parameters are from one homogenous hypothetical patient population. All assumptions made in a model-based economic evaluation need to be clearly stated and justified.

Recommendations for the choice of the most appropriate modelling technique can be found in the ISPOR-SMDM Modeling Good Research Practices (Caro et al., 2012) (see Section 13).

3. Target Population

Target population is the patient population for which the intervention is intended for in clinical practice. To ensure relevance, local epidemiological data should be used to describe patient population as well as the relevant subgroups. Details of the target population should be described, usually in term of age, gender, different prognosis, socioeconomic status, comorbidities and risk factors. Subgroup analysis is recommended whenever there is suspicion of heterogeneity in the group that can impact cost or effectiveness of treatment (e.g. stratified analysis between men and women, young adults and elderly, and intermediate and advanced stage of disease).

4. Perspective

Perspective is the point of view adopted when deciding the types of costs and health benefits to be included in an economic evaluation. The choice of perspective is determined by the context of the study, persons or institutions affected by the outcome of interest, and those that bear the costs of the intervention. In particular, the perspective will be implied by the question to whom the economic evaluation is intended to provide an answer. It should be consistent for both cost and outcome components.

In Pharmacoeconomics, an evaluation can be conducted from the perspective of either the healthcare provider, payer, patients or society. Narrowing the scope to the Malaysian public health care system, the MoH is regarded as the healthcare provider and also the payer (similar to budget holder in the context of BIA) who bears healthcare cost. Thus, an economic evaluation which is conducted for the purpose of submission to the MoH should be conducted from the MoH's perspective.

5. Time Horizon

The time horizon of the analysis should be long enough to capture all changes in costs and outcomes of the interventions being analysed. In short, it should reflect the natural history of the disease. In addition, long-term and lifetime analysis using extrapolated or modelled data is allowed with clear reporting and justification.

6. Selection of Comparator(s)

The intervention to be assessed should be compared against the most relevant alternative(s) for the proposed indication in the applied setting. The choice of comparator(s) must be justified as it will critically determine the relative cost-effectiveness of the new intervention and the relevance of the assessment to the healthcare decision makers. The most relevant alternative(s) should be the standard intervention(s), either based on the Malaysian Clinical Practice Guidelines or Standard Treatment Guidelines. When one of these is available, the usual treatment or routine care, either medical or non-medical treatment, best supportive care or symptomatic care can be used as comparator(s) with justification involving consultation of expert opinion. Off-label treatment should not be used as a comparator unless there is sufficient evidence of its use, clinical safety and efficacy.

Commonly, the comparator(s) is (are) the treatment(s) that most prescribers or clinicians would replace with the new intervention. In some cases, the comparator(s) is (are) the current treatment that is most widely used by patients. Multiple comparators can be included in the analysis. In case of an add-on intervention, the current treatment without the added intervention can be used as the comparator.

Alternatively, an efficiency frontier can be constructed. This involves the identification of all relevant treatments for the targeted indication and population, the removal of dominated or extendedly dominated interventions from the list of relevant comparators, and the calculation of the ICERs of all interventions compared to the next best alternative.

7. Retrieval of Effectiveness Evidence

Effectiveness data used in an economic evaluation is prioritised based on the hierarchy of evidence. Studies with the highest possible level of evidence i.e. RCTs, systematic reviews and meta-analyses of RCTs should be given precedence. Ideally, data from locally conducted RCTs of sufficient quality and with a direct comparison are preferred. In the absence of these local data, the economic evaluation should be based on quantitative clinical and safety evidences which are obtained via a systematic review of the literature.

7.1 Systematic Literature Review

A comprehensive and systematic literature review must follow all the methodological standards, pre-defined protocol, reproducible search strategy and transparent selection criteria. The process, as the name suggests, should be systematic and complete, and it aims at preventing bias as much as possible. The quality of all the studies included should be critically appraised and reported.

7.2 Search Strategy

Details of the search strategy used to retrieve clinical studies should be described (in the Appendix), including the:

- medium used to conduct the search and the person who conducted it;
- databases searched;
- time when the search was undertaken;
- any publication date or study design restrictions; and
- search strategy, keywords or Medical Subject Headings (MeSH) used.

The pre-defined inclusion and exclusion criteria used for selecting relevant studies should be clearly specified. The report should clearly state the reasons for excluding any studies. The methods used to analyse or combine data should be clearly outlined and justified.

7.3 Source of Clinical Data

Key clinical data sources to be used when estimating relative treatment effects include published randomised controlled trials (RCTs), meta-analyses and observational studies. The preferred sources of clinical data for pharmacoeconomic studies are from the RCTs. Meta-analyses of RCTs are used when it involves more than one key study or when there are conflicting findings among the studies. In the absence of valid RCTs, evidence from the highest available level of study design should be considered (i.e. from unpublished trial data, expert opinion, post-surveillance studies or case reports) with reference to the limitations of the study design.

The key preferred clinical data sources are as follows:

i. Systematic Reviews and Meta-analyses

It is recommended that clinical effectiveness data to be used in a model-based economic evaluation are obtained from systematic reviews and meta-analyses, provided that these are of sufficient quality i.e. only high quality RCTs are considered.

ii. Randomised-controlled Studies

According to the hierarchy or levels of evidence, in the absence of a systematic review and meta-analysis, clinical data could be obtained from individually conducted RCTs. In theory, well-designed and well performed (i.e. double-blinded) RCTs have the least probability of confounding effect and consequently, carry the highest degree of certainty about the causal relation between the intervention and the observed effect.

iii. Non-randomised studies/ Observational

In cases when data from RCTs are not available, or the results from RCT have limitations; for example, in situations when it involves acute or progressive

condition or rare disease or when result of an intervention in real practice are needed for example, in case when there is a clear dose-response relation of an intervention, data from non-randomised/ observational studies are sufficient or even preferred. Non-randomised/ observational studies include cohort, case cohort and cross-sectional studies. When non-randomised studies/ observational studies are utilised, potential bias must be fully explored, reported and taken into account in the economic evaluation.

7.4 Direct versus Indirect Comparisons

A direct, head-to-head comparison is recommended when performing evidence synthesis. This approach produces the most reliable evidence and should be used even if only a single randomised study of sufficient quality with a direct comparison is available.

However, in the case where no direct comparative study is found, indirect comparative studies may be used, in which the results of different studies are compared with each other. However, these studies should be carefully selected to prevent bias as much as possible. The use of proper methods for integrating indirect comparisons in a single quantitative analysis such as the Bayesian or frequentist which is a mixed treatment comparison (MTC) or a network meta-analysis is highly recommended.

7.5 Placebo-Controlled Studies

In principle, placebo-controlled studies are not recommended to be used in economic evaluations because in clinical practice, placebo is not considered as a standard or usual care. Nevertheless, placebo-controlled studies may be included in a mixed treatment comparison or in a network meta-analysis to complete the network. If placebo is taken to be a proxy for best supportive care, this approach should be well justified.

7.6 Source for Obtaining Data

Information on clinical efficacy can be obtained from, but not limited to, several sources such as MEDLINE, EMBASE, Cochrane and Evidence-Based Medicine (BMJ Journals). Additionally, cited references and handsearching can be done to ensure the comprehensiveness of the search.

Information on local drug safety and international regulatory authorities can be obtained from the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) through the National Pharmaceutical Regulatory Agency (NPRA). Alternatively, online sources of international safety bodies such as Medsafe, Food Drug Administration (FDA) and European Medicines Agency (EMA) may be utilised.

Furthermore, information on international registries of clinical trials can be found at ClinicalTrial.gov website (www.clinicaltrial.gov/). It may also be useful to refer to the reviews undertaken by health technology assessment organisations listed in Table 7.

Table 7: List of health technology assessment organisations

Organisations	URL
Malaysian Health Technology Assessment Section	http://www.moh.gov.my/index.php/pages/view/1691
National Institute for Health and Care Excellence (UK)	http://www.nice.org.uk/
NIHR Health Technology Assessment Programme (UK)	http://www.hta.ac.uk/
Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca/
Scottish Medicines Consortium	http://www.scottishmedicines.org.uk/
Australian Pharmaceutical Benefits Scheme	http://pbs.gov.au/

Organisations	URL
Belgian Health Care Knowledge Centre	http://kce.fgov.be/
Swedish Agency for Health Technology Assessment and Assessment of Social Services	http://www.sbu.se/en/
All Wales Medicines Strategy Group	http://www.wales.nhs.uk/sites3/homecfm?orgid=371

8. Measuring Outcomes

8.1 Types of Outcomes

Health outcomes are consequences of treatment or intervention which result in changes of health. There are two types of outcomes:

- Intermediate outcomes
  Common and typically on the causal pathway to the final outcomes
- Final outcomes
  Reflect how patients feel and function or how long they survive

For example, HbA1c is an intermediate outcome whilst mortality is the final outcome for diabetes disease.

The choice of outcome depends on the study question and also the disease. Commonly, the type of economic evaluation depends on the type of outcomes measured in the study.

8.2 Outcome Measures in Cost-Effectiveness Analysis

As mentioned in the previous section, outcomes are measured in natural units in CEA. In other words, the outcomes in the analysis should be consistent with the results of the clinical intervention. Therefore, if an intervention has an impact on

mortality, then the outcome should be expressed in the number of life years gained; however, if an intervention has an impact on symptom control, then the outcome should be expressed in the number of symptom-free days gained. In cases where only intermediate outcomes are available but the final outcomes are considered important for an economic evaluation, modelling may be necessary.

8.3 Outcome Measure in Cost-Utility Analysis

The preferred outcome measure in CUA is QALY. It assumes that health is a function of length of
life and quality of life. The relationship between these two factors is as depicted below:

Quality-adjusted Life Years = *Health-related Quality of Life* x *Number of Life Years*

One QALY is equivalent to one year of perfect health. The outcome measure using QALY is preferable for the following conditions:

- When health-related quality of life (HRQoL) is the/an important outcome;
- When the intervention affects both morbidity and mortality, and a common unit of outcome is needed;
- When the interventions compared have a wide range of outcomes, and a common unit of output is needed for comparison;
- When an intervention is compared to others that have already been evaluated using CUA;
- When dealing with a limited budget situation such that the decision makers must determine the programmes/services to reduce or eliminate to free up funding for the new programme; and
- When the objective is to allocate limited resources optimally by considering all alternatives and using constrained optimisation to maximise health gains achieved.

The HRQoL in the context of QALY refers to a valued/weighted-HRQoL, which is also known as utility; 'valued-HRQoL' will be used henceforth. The valued-HRQoL score of 1 represents a state of perfect health while the valued-HRQoL score of 0 represents death.

8.3.1 Valuation methods of HRQoL

There are various tools to measure the HRQoL of patients; these can be categorised based on the scope of their construct (generic vs specific), or how the construct is developed (non-preference vs preference). Only preference-based tools are capable of producing a valued-HRQoL suitable for CUA as they provide a single value or an aggregate score that represents multiple components of HRQoL such as mobility, sleep and ability to carry out daily activities. There are two types of preference-based tools: indirect and direct types (Figure 1).

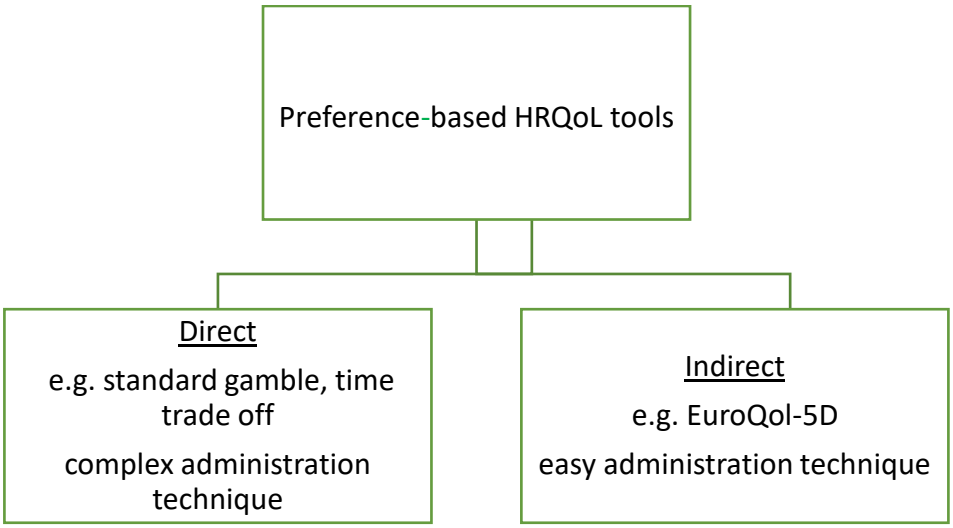

Figure 1: Types of preference-based HRQoL tools

Indirect preference-based tools indirectly measure preferences by scoring the patients' descriptive responses using pre-determined weightages (utility values). The preferred tool for measuring preference is EuroQol-5D (EQ-5D). It is strongly recommended to use locally pre-determined

weightages i.e. original Malaysian set of EQ-5D utility values (Shafie et al., 2019), in order to obtain valued-HRQoL. Using the EQ-5D and the same set of utility values across all economic evaluations greatly facilitate cross-comparisons among different disease areas.

In cases where appropriate valued-HRQoL could not be obtained through EQ-5D, direct measurement tools can be used with appropriate justifications. Examples of such tools are Standard Gamble (SG) and Time-Trade Off (TTO)(Figure 2).

Standard Gamble (SG):

- Briefly, in SG, patients are asked to choose between remaining in a state of ill health for a period of time, or choosing a medical intervention which has a chance of either restoring them to perfect health or causing them to die.

Time-Trade Off (TTO):

- In TTO, patients are asked to choose between remaining in a state of ill health for a period of time, or being restored to perfect health but having a shorter life expectancy.

Figure 2: Direct measurement tools

9. Resource Use and Cost

9.1 Cost Components based on Resource Use

The cost components to be included in economic evaluation will depend on the resource use and this is based on perspective of the evaluation. The following perspectives should include the use of resources and their associated costs:

Table 8: Resource use and associated costs based on the perspective taken in economic evaluation.

Cost Components		
Healthcare Provider	**Payer**	**Society**
All direct costs relevant to the provision of the service by the provider Examples of resources use: • diagnostic procedure • medicine • monitoring • clinic visit • hospital admission	All direct costs relevant to the services borne by the payer Could be similar to resources use as listed for health provider depending on the coverage of costs borne by the payer.	All direct and indirect costs relevant to society including cost of obtaining care and opportunity costs. Examples of resourses use: • diagnostic procedure • medicine • monitoring • clinic visit • hospital admission • transportation • food • accommodation • over the-counter purchases

9.2 Sources of Cost Data (Resource Valuation)

Cost data can be obtained from published literature or by primary data collection of local unit cost for all resources used. Examples of sources of valuation are the Malaysian Fee Act, facility-specific price/ finance database, and other relevant sources including expert opinion in the absence of published data. As for medicine prices, references include the MoH Consumer Price Guide which can

be accessed via the official website of Pharmaceutical Services Programme, IQVIA databases and also local purchase order at facilities.

Apart from that, local casemix costs are also available from the MoH and casemix centres in a few local universities including Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and Universiti Sains Malaysia. Under the MoH, the Hospital Management and Services Unit (Casemix System Subunit) was established in 2010. Casemix System in MoH was developed as a patient classification tool which groups patients with relatively homogenous resources and clinical characteristics for each group using MalaysianDRG software V2 2016. It consists of a Clinical module, Costing module, Malaysian Health Mortality Information System module, Pay-for-Performance module and Executive Information System (EIS) module. The main output retrievable from EIS module includes Major Diagnostic Category, Diagnosis Related Group (DRG), treatment cost per DRG, severity of illness and Casemix Index (hospital efficiency index). The MoH Casemix System is accessible with a valid user account according to user access requirements and roles. Casemix data can also be requested on an ad hoc basis. A guideline for data request is currently under development and expected to be released in year 2020.

9.3 Costing Method

The costing method used to generate cost data should be clearly reported. The general steps in a costing exercise are listed below:

i. Identification of resources use (cost components)
ii. Measurement/ quantification of resources use (number of resources use)
iii. Valuation of resources (cost per unit)
iv. Multiplying the cost per unit and number of resources use

The price year of all relevant unit costs should be reported and adjusted to the price year of the evaluation. All costs reported in other currencies must be converted appropriately to Malaysian Ringgit.

Theoretically, the types of costing method can be broadly categorised into two approaches: the micro-costing and macro-costing.

- Micro-costing approach provides accurate and detailed cost information in which it quantifies and costs out every cost component consumed in an intervention. Micro-costing approach can be applied in cases where an intervention does not have established average costs, or costs of intervention vary.

- Macro-costing or gross costing approach provides aggregated cost data. It is often used when fine detail is not available. In circumstances where researchers are limited to macro-costing, it is important to be aware that the resulting costs may not reflect the true costs to the healthcare system.

The difference between these costing methods can be seen from the example of cost components used to obtain hospitalisation cost. By using the micro-costing method, cost components can be inclusive of costs for personnel time, bed, food, linen, medicines, diagnostics and blood test. On the other hand, by using the gross costing method, cost for in-patient days can be used to represent all the cost components calculated in the micro-costing method.

The research question and availability of cost data will determine the choice of approach i.e. between micro-costing and macro-costing. Many studies often combine both approaches in which the micro-costing approach is used for the direct costs of the intervention, whereas macro-costing is used for resources that are less relevant to the disease and health services.

10. Discounting for Future Outcomes and Costs

Costs and health outcomes that could occur in the future should be discounted to present values. This is to account for the time value of money and the delay in achieving the health benefits. In a study longer than a year, annual discount rate of

3% should be adopted for both costs and outcomes. Nonetheless, sensitivity analysis with higher and lower discount rates (for example 0% and 5%) should be conducted.

11. Presentation of Results

The total costs and health consequences of all alternatives being considered should be reported separately to provide a clear view on economic and health consequences of each intervention. Base case results can be presented as a table of costs (itemised by different types of cost), and outcomes of all the alternatives considered. Aggregate and disaggregate results on costs, outcomes and cost-effectiveness ratio should be presented to provide information about the new treatment or intervention at individual and population levels.

11.1 Incremental Cost-effectiveness Ratio (ICER)

The ICER compares the differences between costs and health outcomes of two alternative interventions (Figure 3). It reflects the additional (incremental) cost per additional unit of outcome achieved. For ease of interpretation, graphical presentations such as cost-effectiveness planes may be used.

$$\text{ICER} = \frac{\text{Cost}_1 - \text{Cost}_0}{\text{Effectiveness}_1 - \text{Effectiveness}_0}$$

where :
- Cost_1 = the cost of the new treatment
- Cost_0 = the cost of the current treatment (comparator)
- Effectiveness_1 = health consequences of the new intervention
- Effectiveness_0 = health consequences of the comparator

Figure 3: ICER Formula

11.2 Cost-effectiveness Threshold

Cost-effectiveness threshold (CET) helps to inform decision makers what represents an approximate value for money i.e. an acceptable ICER, given the local budget constraints in a particular healthcare system. An explicit threshold may lead to rigidity in the decision-making process and manipulation of drug prices. However, it is good as it makes the decision rules clearer thus, making the decision-making process more transparent and justifiable. Nevertheless, there is no hard-and-fast rule with regard to having an explicit CET in a country. Sweden and France, for example, prefer to keep their CETs implicit. Similarly, in Malaysia, the threshold for MOH funding decisions is not made explicit by the decision makers.

Currently, there is an approach that adopts the Gross Domestic Product (GDP) per capita threshold as recommended by the WHO Commission on Macroeconomics and Health. An intervention that is less than 1 GDP is considered to be cost-effective and has higher probability to be funded. This CET corresponds to the current value (at the time of writing) which is around RM 42,000. However, this human capital approach is commonly argued as its origin is heuristic and not based on a clear empirical estimate (Thokala et al., 2018). More recently, the WHO seems to be trying to dissociate from this initial recommendation as it does not fit many contexts and has been misused. However, GDP-based threshold could still be used to indicate interventions which a country may consider but not to dictate any funding decision (World Health Organization, 2016).

Alternatively, there is a published study which estimated Malaysian CET using Willingness-To-Pay (WTP) approach. This study reported Malaysian WTP threshold to range between RM 19,929 and RM 28,470 (Lim et al., 2017). An intervention is considered cost-effective if its ICER lies within this range. Establishing CET using WTP approach utilises the information of individual or societal monetary valuation of health gain. However, this approach has also been argued as it does not reflect opportunity costs and is detached from the constrained budget setting.

As each approach of CET estimation has its own pros and cons, there are still on-going debates on the best CET to adopt by healthcare systems. Because it is implicit in Malaysia, researchers are free to quote any CET deemed appropriate in their local economic evaluations. Ultimately, the decision as to whether an intervention is cost-effective or not lies within the hands of the decision makers.

12. Sensitivity Analysis

Sensitivity analysis explores the uncertainty and robustness of the results in an economic analysis. It should systematically examine the influence of different variables/parameters and assumptions to identify the key parameters with greatest effect on the results. Several sensitivity analysis methods can be used such as the one-way, multi-way, scenario and probabilistic sensitivity analysis (PSA) (Figure 4).

One-way sensitivity analysis

- Examines one parameter at a time. Results of this analysis should be presented in a tornado diagram.

Multi-way sensitivity analysis

- Examines multiple parameters at a time.

Scenario sensitivity analysis

- A type of multi-way analysis that combines certain parameters that reflect a particular scenario. Typically,the best case scenario and the worst case scenario are chosen.

Probabilistic sensitivity analysis (PSA)

- Uses probability distributions over specified ranges for the key parameters and can draw samples at random to generate a distribution of the ICER. This is a preferred method. Where possible, results of PSA should be presented in the form of a cost-effectiveness acceptability curve (CEAC).

Figure 4: Examples of several types of sensitivity analyses

13. Modelling

A model is a mathematical framework representing some aspects of reality at a sufficient level of detail to inform a clinical or policy decision. Simple decision tree and Markov model are the two common types of model for economic evaluations. Good modelling practices (Caro et al., 2012) should be followed when constructing the model used to conduct the evaluation. Primarily, the model structure should be appropriate and validated to address the study question. The model should be built in a way that allows the results to be updated as more data become available. Descriptions of the model should include its scope, structure and underlying assumptions (with justifications). Any causal relationships and extrapolation

techniques used in the model should be explained, justified and tested through sensitivity analysis.

Data inputs should be systematically identified, collected and assessed before these can be incorporated into the model. Appropriate methods should be used to analyse or combine data from different sources. However, data that come in the form of expert opinion should be used with caution as it is the lowest level source of evidence. Nevertheless, sources of these data inputs and their quality should always be identified and reported.

14. Generalisability

Generalisability refers to the extent to which the results of a study hold true for other population and/or in a different context. It is an important consideration as it enables readers to assess the applicability of the results to their practice. As such, an economic evaluation should

- describe the population criteria;
- highlight potential differences;
- extensively analyse the sensitivities of key parameters;
- clearly state underlying assumptions;
- identify potential limitations;
- explore the variability and uncertainty within the study through sensitivity analysis;
- account for differences in currencies, prices, tariffs and consumption of resources (that may differ across different health systems); and
- interpret inconclusive data with conservative assumptions especially when there is high uncertainty on:
  - long term benefits of a treatment,
  - correlation between surrogate measure and clinical outcomes,
  - effectiveness of treatment (due to low-quality evidence e.g. non-RCT),
  - relevance of evidence to Malaysia (poor external validity of trials), and
  - incremental effectiveness of treatment.

15. Reporting

It is recommended that the economic evaluation report follow the CHEERS checklist by Husereau et al., 2013. There are 6 main sections of the report: (1) title and abstract; (2) introduction; (3) methods; (4) results; (5) discussion; and (6) others. Table 9 below lists all the details for each of the sections.

Table 9: Format for reporting result for an economic evaluation

No.	Section	Item(s)
1	Title and abstract	Title Abstract
2	Introduction	Background and objectives
3	Methods	Target population and subgroups Setting and location Study perspective Comparators Time horizon Discount rate Choice of health outcomes Measurement of effectiveness Measurement and valuation of preference-based outcomes Estimating resources and costs Currency, price date, and conversion Choice of model Assumptions Analytic methods
4	Results	Study parameters Incremental costs and outcomes Characterising uncertainty Characterising heterogeneity
5	Discussion	Study findings Limitations

No.	Section	Item(s)
		Generalisability Current knowledge
6	Other	Source of funding Conflicts of interest

B. BUDGET IMPACT ANALYSIS

BIA estimates the financial consequences of adopting a new health intervention in a clearly specified setting. It helps to inform the budget holders of the overall impact of the new health intervention to the budget. In a way, it complements pharmacoeconomic evaluations by demonstrating the affordability and sustainability of a health intervention in a given setting. The key elements of a BIA include the estimated size of eligible population, perspective, time horizon, the current and future treatment mix, the drug-related and disease-related cost of the treatment mix and uncertainty analysis (Mauskopf et al., 2016).

1. Eligible Population

All patients who are eligible for the new intervention during the time horizon of interest should be included as the population in BIA. The number of patients may be estimated based on the locally approved indications for the new treatment or intervention. It needs to reflect any planned restrictions on the use as well as the predicted uptake and market effects (a new intervention sets in motion of various marketplace dynamics, including product substitution and potential market expansion). It is also important to consider the proportion of the eligible population in different subgroups defined by disease severity.

2. Perspective

A BIA is performed from the perspective of the budget holder (or the paying party) who will bear the financial consequences of the new or optimised healthcare intervention or the abandonment of existing healthcare. In the context of BIA prepared for submission to the MoH, it should be carried out from the perspective of the Ministry.

Additionally, the BIA needs to be flexible in order to generate estimates which may include various combinations of health care, social services and other costs. With a flexible design, the BIA will be able to show decision makers not only the budget

impact, but also the larger economic implications of the introduction of the new intervention.

3. Time Horizon

A BIA should be presented in a time horizon relevant to budget holders—in accordance with their budgeting cycles and periods (e.g., monthly, quarterly and annually). More importantly, the time horizon should permit obtaining a result that is useful for the budget holders.

A time horizon between 3 and 5 years is recommended to make projections of budget impact (market changes expected to reach a steady state in 3 years). The annual budget impact should be calculated from the time the new intervention is introduced while considering the expected market penetration to occur during that period. Although a time horizon that goes beyond a few years requires considerable assumptions, it may be necessary if the expenditure is likely to undergo changes over the years (e.g. treatment of chronic diseases and savings on the long term) or to illustrate the off-setting disease cost savings from the intervention that may occur in future years (e.g. interventions that cure chronic hepatitis and, thus, prevent liver cirrhosis or liver cancer that tends to occur far in the future).

4. Treatment Mix

Treatment mix is defined as the combination of all treatments that are being used to treat a particular condition. Current treatment mix consists of all existing treatment options whereas the projected (future) treatment mix consists of both the new intervention and the remaining treatment options. In a BIA, the future treatment mix will be compared against the current treatment mix.

The proportion of patients on the various treatment options will differ between the current mix and the projected treatment mix once the new intervention is introduced. The current treatment which is most likely to be replaced by the new treatment can be identified through surveys of clinical expert opinion, database analyses or patient

medical records. Alternatively, Malaysian clinical guidelines can be used to predict the replaceable treatments.

5. Drug-Related Cost

All direct costs relevant to the services funded by the payer (MoH) should be included. Identification of cost should be according to the perspective of the payer. The resources use should reflect the actual or estimated usage within a clinical practice. More importantly, the resources use and associated costs should be relevant to the health condition and intervention of interest over the chosen time horizon. The payer's perspective does not include productivity loss and out-of-pocket expenditure.

5.1 Cost of Current Intervention Mix

To assess the cost of the current intervention mix, the cost of the intervention is multiplied by the number of patients in each population subgroup. The costs should include the intervention acquisition cost, administration, monitoring or any other procedural costs. It should also include the cost of follow-ups over the time horizon and any resource cost in managing side-effects.

5.2 Cost of Future Intervention Mix

Costing of the future intervention mix follows the same process as the current mix except that for technologies that are not yet available in the market, the price may have to be assumed if it is not set yet. In this case, the assumed intervention cost should be transparent and justified. Any uncertainty with regard to the price should be considered in the alternative scenarios for the sensitivity analyses.

6. Disease-Related Cost

Alternative intervention mix is likely to result in changes in the symptoms, duration or disease progression rates associated with the health condition; thus, it is likely to create changes in the use of all other condition-related healthcare services. All the

costs associated with these changes should be computed as they will have an impact on the health plan budget. The impacts of the new intervention on productivity, social services and other costs outside the healthcare system are not routinely considered in a BIA as they are generally not relevant to the budget holders. However, these aspects may be of importance if the BIA is intended to inform other agencies such as private health insurers or employers.

6.1 Disease-related cost of Current Intervention Mix

Costs to be included should reflect the impact of current intervention mix on prognosis, disease severity and relevant clinical outcomes.

6.2 Disease-related cost of Future Intervention Mix

Costs to be included should reflect the impact of future intervention mix on prognosis, disease severity and relevant clinical outcomes.

7. Uncertainty analysis

There are two types of uncertainty that are relevant to BIA: parameter uncertainty in the input values used and structural uncertainty introduced by the assumptions made in framing the BIA. Examples of parameter uncertainty are costs, population, efficacy and safety estimates, while examples of structural uncertainty are market shares of treatment mix and pattern of uptake.

Parameter uncertainties can be addressed using standard approaches such as the one-way sensitivity analysis by substituting inputs with ranges of values. These ranges are best to be obtained from literature review or expert opinions.

Structural uncertainties are normally addressed by scenario analyses, whereby alternative “plausible scenarios” are produced by changing input parameter values and/or structural assumptions.

8. Presenting Budget Impact

A budget impact analysis is presented following the recommendations by the ISPOR Taskforce 2012 (Sullivan et al., 2014).

Table 10: Key features in presenting results of budget impact analysis

Key features in presenting the results of budget impact analysis
1. Introduction • Study objectives & perspectives • Epidemiology and management of health problems • Clinical impact • Economic impact 2. Study design and methods • Patient population • Intervention mix • Time horizon • Perspective • Analytic framework description • Input data • Data sources • Data collection • Analyses • Uncertainty 3. Results 4. Conclusion and limitations 5. Inclusion of graphic and tables • Figure of analytical framework • Table of assumptions • Table of inputs • Table of outputs • Schematic representation of uncertainty analyses 6. Appendices and references

C. APPENDICES

Table 11: Key features for the guidelines

Key Features	
Title and year of the document	Pharmacoeconomic Guidelines for Malaysia 2019
Affiliation of members	PSP, MOH, USM, UM, UiTM, UKM, CUCMS, Monash University Malaysia
Purpose of the document	To update on the methodological guidance and to serve as a standard for conducting economic evaluation in Malaysia
Standard reporting format included	Yes
Disclosure	Yes
Target audience	Researchers, pharmaceutical companies, health economists and health professionals both in the public or private sectors
Perspective	No restriction. Payers or budget holders are encouraged.
Indication	Indication must be approved by the Drug Control Authority (DCA) or reference country.
Target population	Must be clearly stated
Subgroup analysis	Yes. Included when appropriate
Choice of comparator	Yes. Most relevant alternative(s) for the proposed indication.
Time horizon	Choice must be justified. Should be long enough to capture all outcomes and costs of intervention
Assumption required	Yes
Preferred analytical technique	CEA and CUA. Choice must be justified.
Costs to be included	All relevant costs depend on the study perspective
Source of costs	Local unit cost data
Modelling	Yes

Key Features	
Systematic review evidence	Yes. Preferred clinical evidences from RCT and meta-analysis
Preference for effectiveness over efficacy	Not stated
Preferred outcome measure	Natural units for CEA; QALY for CUA
Preferred method to derive utility	EQ-5D
Equity issues stated	Not stated
Discounting costs	3%
Discounting outcomes	3%
Sensitivity analysis-parameters and range	Not stated
Sensitivity analysis-methods	One-way, multi-way, scenario and probabilistic sensitivity analysis
Presenting results	Yes
Incremental analysis	ICER
Total cost-effectiveness ratio	ICER
Generalisability	Yes
Budget impact analysis	Yes
Mandatory or recommended or voluntary	Recommended

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